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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,752		Johannes Jacobus Voorberg	294-86	5298

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,752	VOORBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-59,67,68,70-73,76-80 and 82-86* is/are pending in the application.

4a) Of the above claim(s) *19,21-59,80 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,20,67,68,70-73,76-79,85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/18/05 has been entered.

2. Claims 17-59, 67, 68, 70-73, 76-80 and 82-86 are pending.

3. Claims 19, 21-59, 80 and 82-84 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 17, 18, 20, 67, 68, 70-73, 76-79, 85 and 86 are under examination as they read on an a polypeptide capable of specific bindign to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the variable region of the heavy chain of a human antibody with factor VIII specificity or parts thereof which at least includes the CDR3 region and a pharmaceutical composition thereof and DP-10 ans the species.

5. In view of Applicant's argument and the evidance presented in Figure 7A, of the neutraliztion of the inhibitory activity of the murine monoclonal antibody CLB-CAg 117 by scFv-EL14, wherein increaseing amounts of scFv-EL14 were capable of neutralizing the inhibitory activity of CLB-CAg 117 and that a conscentration of 0.75 ug/ml suffices to restore factor VIII activty to its origninal level have obviated the previous rejection under 35 U.S.C. 112(1st) with respect to the pharmaceutical composition.

6. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

7. Claims 17, 20, 67-68, 70-73 and 76-79 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 17, 20, 67-68, 70-73 and 76-79, as written, do not sufficiently distinguish over polypeptides (autoantibodies) as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" as disclosed on page 5, lines 23-24 of specification. See MPEP 2105.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is improper to recite "A" composition in claim 18. It is suggested that said word be changed to "The".

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 17, 18, 70-73, 76-79 and 85-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies (Davies et al 1997, thromb. Haemostas. Supplement: 2352).

Davies et al teach eight human FVIII specific scFvs were selected by panning on immobilized rFVIII. Further, Davies et al teach obtaining the immunoglobulin V(ariable) domain structure of immune FVIII antibodies obtained by V gene phage display technology from 3 Haemophilia A patients with peak inhibitor levels about 60Bu/ml. Davies et al teaches that 3 patients have antibodies against the A2 domain (heavy chain is A1-A2-B) and 2 patients have antibodies to the light chain (A3-C1-C2). Davies et al teach the method of producing a recombinant scFvs specific for Factor VIII by obtaining the primary structure of the variable domains of factor VIII antibodies obtained from inhibitor patient B cells RNA by V gene phage display technology. The VH gene cDNA was obtained by reverse transcription of lymphocytic RNA from the 3 patients with an IgG specific primer and amplified by the PCR with appropriate VH and joining gene primers. The amplified VH gene repertoire was cloned for display as single chain V domain fragments (scFv) on the surface of the phagemid vector PhEN-2-VL. Each library contained 10^7 individual clones (see the abstract in particular). Davies et al isolated 8 human FVIII specific scFvs.

Claim 72 is included since the reference human scFvs bind to A2 domain of factor VIII, then the antibody would also bind the heavy chain of factor VIII consisting of the A1 domain, the A2 domain and the B domain of factor VIII.

While Davies et al teachings may be silent as to the "interference with the activity of factor VIII inhibitors" in claim 17, "wherein the polypeptide reduces the activity of factor VIII inhibitors of haemophilia A patients" in claim 76, and wherein " the factor VIII inhibitors of Haemophilia A patients are antibodies specific for factor VIII" in claim 77 per se; the referenced svFv polypeptides are the same as the claimed polypeptide that is capable of specifically bind to

FVIII, wherein the scFvs were obtained from Heamophilia A patients with peak inhibitor levels about 60Bu/ml. Therefore, said limitations are considered inherent properties of the referenced scFv polypeptides.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference scFvs does not interference with the activity of factor VIII inhibitors recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 1/18/05, have been fully considered, but have not been found persuasive.

Applicant submits that the present invention interfere with the activity of factor VIII inhibitors. However, Davies et al is completely silent about whether the disclosed scFv's are capable of interfering with the activity of factor VIII inhibitors. Further, Applicant submits that not all scFv's to factor VIII have the claimed property in Davies et al to select scFv polypeptides that have this claimed property. Applicant also argues that the publication of Davies et al is only an abstract, which did not lead to a publication. In addition the abstract of Davies et al does not provide an enabling disclosure for scFv's that are capable of interference with the activity of factor VIII inhibitors. Applicant concludes that the claimed invention cannot be said to be anticipated by Davies et al.

However, Applicant does not provide objective evidence to distinguish the prior art from the claimed invention. A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed in invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). See MPEP 2121.01.

Furthermore, a chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Similarly, when a claim recites using an old composition or structure (e.g. a polypeptide capable of specific binding to factor VIII comprises a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody) and the use is directed to a result or property of that composition or structure (interference with the activity of factor VIII inhibitors), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52

USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al in view of U.S Patent No. 4,731,245 (of record).

The teachings of Davies et al reference, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a composition with a pharmaceutically acceptable carrier in claims 20.

The `245 patent teaches a composition comprises the antibody, as the active ingredient in association with a pharmaceutically acceptable carrier. Advantageously, the composition can be formulated in dosage unit form. The amount of the active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose (see col., 7 line 63 through col., 8 line 3 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the antibody fragments taught by Davies et al in a composition with a pharmaceutically acceptable carrier as taught by the `245 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the composition can be formulated in dosage unit form. Further, the amount of the active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose as taught by the `245 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 1/18/05, have been fully considered, but have not been found persuasive.

Applicants submit that they have provided arguments to address the rejection of claims 17 and 18 over Davies et al. Applicant concluded that claim 20 is patentable over Davies et al at least for the same reasons that claims 17 and 18 are patentable. Applicants submit that there is not recognition in Davies et al to select for polypeptides that have the activity of the claimed polypeptides (i.e., interference with activity of factor VIII inhibitors). Applicants concluded that the combination of Davies et al and the `245 patent does not result in the claimed invention.

However, the Examiner's position is the same as indicated under 35 U.S.C 102(b) rejection. Further, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the antibody fragments taught by Davies et al in a composition with a pharmaceutically acceptable carrier as taught by the `245 patent to enable the administration of the antibody at a daily dose as taught by the `245 patent.

13. Claims 17 and 67-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al in view of Foung et al 1986 and U.S Pat. No. 5,916,771.

The teachings of Davies et al reference, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation that the human antibody is an IgG in claim 67 from subclass IgG4 in claim 68.

Foung et al teach the generation of human monoclonal antibodies by fusion of EBV-activated B cells to a human-mouse hybridoma. Foung et al have developed a strategy to produce antigen-specific human monoclonal antibodies which involves initial EBV activation and expansion of the antigen-specific B-cell production, and subsequent fusion to a human-mouse hybridoma cell line (see page 169, Figure 1 and 2nd paragraph in particular). Finally, Foung et al teach that the combination of stability and specificity achieved with the system will be important factors in facilitating wider clinical applications of human monoclonal antibodies (see page 174, last paragraph in particular).

The `771 patent teaches that for treating an autoimmune disease, it may be important that the antibody only block binding of a ligand to a receptor and not cause cell killing (no cellular cytotoxicity or complement fixation). In this case, an IgG4 antibody would be preferred. Thus, even in a situation where a high affinity, antigen-specific, fully human antibody has been isolated, it may be desirable to re-engineer that antibody and express the new product in a different cell (see col. 2, line 65 through col., 3 line 12 in particular).

Given that haemophilia A is an autoimmune blood disorder, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to generate human monoclonal antibodies as taught by Foung et al with subclass IGG4 as taught by the `771 patent using the target B cell epitopes localized on the A2 and C2 domains from a haemophilia A patients with peak inhibitory levels above 60 Bu/ml as taught by Davies et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because IgG4 exhibit no cellular cytotoxicity or complement fixation in treating autoimmune diseases as taught by the `771 patent. Further, because human monoclonal antibodies are important factors in facilitating wider clinical applications as taught by the Foung et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 7, 2005

Maher Haddad

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